

Metabolic modulators as a treatment of atrial fibrillation

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Valorization

Social relevance

In 2010, approximately 33.5 million people were suffering from atrial fibrillation (AF), defining this arrhythmia as the most common rhythm disturbance in clinical practice¹. The burden of AF in Dutch general population amounts to 1.6% and up to 1.8% in the European Union overall². The major risk factors for AF are age, hypertension, heart failure, coronary artery disease, valvular heart disease, obesity, diabetes mellitus, and chronic kidney disease. Taking into account that actual demographic trends suggest a significant increase in the average age of the European Union population it is estimated that the burden of AF is going to be doubled by the year of 2060².

Atrial fibrillation is recognized as an independent predictor of mortality and is associated with many disabling diseases including stroke and heart failure³. It is estimated that one in five strokes is a direct consequence of AF. In addition, patients with AF are more often hospitalized and have a significantly lower quality of life^{4,5}. It is important to note that AF is a chronic disease that needs permanent surveillance and very often constant treatment. Considering the above, it is clear that AF is a disease that causes a significant burden for our health care system, which is going to rise over time.

Current treatment options

Current evidence-based treatment strategies include interventions that aim to restore and maintain sinus rhythm, also named 'rhythm control', or interventions whose main goal is to prevent the development of AF-related complications such as heart failure ('rate control') or the prevention thromboembolic events⁶.

Rhythm control includes drug treatments administered either acutely for pharmacological cardioversion (restoration of sinus rhythm) or chronically for sinus rhythm maintenance. Electrical cardioversion is also used for acute sinus rhythm restoration. Various interventional and surgical ablation procedures that produce scar tissue in the atria and therefore prevent the propagation of fibrillation waves are also recognized as rhythm control treatment strategies⁶.

The development or exacerbation of heart failure as a consequence of AF is mainly related to the high and irregular ventricular activation rates⁷. Therefore, ventricular protection in AF patients requires the maintenance of ventricular rate within a more normal range. This treatment strategy is also known as 'rate control' and includes mainly chronic drug administration to inhibit AV node conduction and in some cases combinations of ablation procedures and pacemaker implantation⁶.

The prevention of the thromboembolic events includes the use of various anticoagulation medication⁸. In some cases, different interventional or surgical techniques can be also used to close or to remove the left atrial appendage which is the most frequent location of emboli^{9,10}.

Although at the first glance the possibilities to treat AF are plentiful, their success rate and especially long-term results are still unsatisfactory. In addition, many of the mentioned treatments are often associated with numerous serious complications and a further reduction in the quality of life of patients with AF.

Cardioversions i.e. restoration of sinus rhythm either by means of pharmacological or electrical cardioversions are highly successful in directly restoring sinus rhythm, but AF recurrence is very frequent¹¹. For sinus rhythm maintenance different antiarrhythmic drugs are used, but prolonged treatment with available antiarrhythmic drugs are often associated with various cardiac and extracardiac side effects¹². This underscored the need for more specific antiarrhythmic drugs that are more atrial-selective and therefore produce fewer side-effects.

Ablation strategies are recommended as the second line of treatment for symptomatic paroxysmal, persistent, and probably long-standing persistent AF patients in which pharmacological SR maintenance was not achievable⁶. Ablation strategies have a better success rate in maintaining SR, but there is no proof that successful ablation would reduce hospitalization or enable discontinuation of anticoagulation therapy. Importantly, the ablation strategies are associated sometimes with life-threatening complications such as death in <0.2% or periprocedural stroke in <1%, while clinically undetectable strokes can be demonstrated in up to 20% of cases^{6, 13}. Together with other less severe complications different ablations strategies should be employed with caution and used only in selected patients.

Prevention of thromboembolic complications such as stroke is mainly achieved with the chronic use of anticoagulation drugs¹⁴. The most common side-effect of long-term anticoagulation is an increase in the incidence of bleeding complications, which in exceptional cases could lead to severe disability or even death¹⁵. It is also important to mention that anticoagulation therapy is also associated with the reduction in quality of life and increased medical costs^{16, 17}.

The novelty of our research

In the first two experimental chapters of this thesis (Chapter 3 and 4) we have investigated two compounds that can be potentially used for the restoration and eventually maintenance of the SR in patients with AF. The advantage of both compounds i.e. ranolazine and pentamidine analog⁶ (PA-6), in a first place is the selectivity of the compounds for atrial tissue and therefore high safety.

The PA-6 is a newly synthesized compound that inhibits I_{K1} . A next step in the development of this compound would be the confirmation of its safety and efficacy in humans.

On the other hand, ranolazine is already a registered drug to treat chronic angina pectoris.

We have provided the proof that ranolazine retains its effectiveness and specificity for atrial tissue at different stages of AF mediated 'electrically remodeled' atria. However, in our study, ranolazine was unsuccessful in restoring SR, but clinical data suggest that it is effective in a group of patients with a recent onset of AF or postoperative AF¹⁸. In addition, ranolazine is safe in patients with the structurally altered hearts and therefore can be considered as an additional therapy for SR maintenance in patients with reduced left ventricular function. Further, because of ranolazine's good safety properties and present approval for long term use, further studies investigating its long term (metabolic) effects in AF are warranted.

Trimetazidine (Chapter 6) is also a drug with metabolism-modulating properties that we have investigated. To the best of our knowledge, metabolic modulation as a long-term treatment option for AF has never been investigated before. We have shown that trimetazidine abolished increased production of reactive oxygen species, and attenuated the hallmarks of structural remodeling observed during AF including cell hypertrophy, interstitial fibrosis, and it preserved mitochondrial shape. Achieving this, trimetazidine could be used as an adjuvant drug, not only in AF patients, but also in the patients at risk for AF.

We believe that patients with new-onset or paroxysmal AF would benefit most from treatment with trimetazidine because it could prevent accumulation of atrial structural alterations leading to arrhythmia stabilization. Preservation of atrial function and structure as a bridge to permanent rhythm control strategies could increase ablation success rate by reducing the complexity of the fibrillation substrate.